# Case Presentation

- A 60 year old male is admitted to the ward with a diagnosis of pneumonia (RLL). On admission his BP 160/90 (at his baseline), temperature of 38.2, RR is 15, and HR 100. Labs are normal except for an ABG 7.41/38/58 SaO2 88%
  - **WHAT IS HIS DIAGNOSIS?**
- One day later he is found to be confused and agitated. Temperature is 38.3, RR 22, HR 125, and BP 110/60.
  - **WHAT IS THE STATE OF HIS CARDIOVASCULAR SYSTEM?**
  - **HOW SHOULD HE BE MANAGED INITIALLY?**
- Following initial therapy the patients BP is 90/60 and he remains confused, agitated, oliguric and has a serum lactate 6.0
  - **HOW SHOULD HIS MANAGEMENT PROGRESS?**
- Five days later the patient remains in the MICU requiring moderate doses of vasopressors to maintain an adequate BP
  - **IS THERE ANYTHING ELSE THAT CAN BE DONE?**

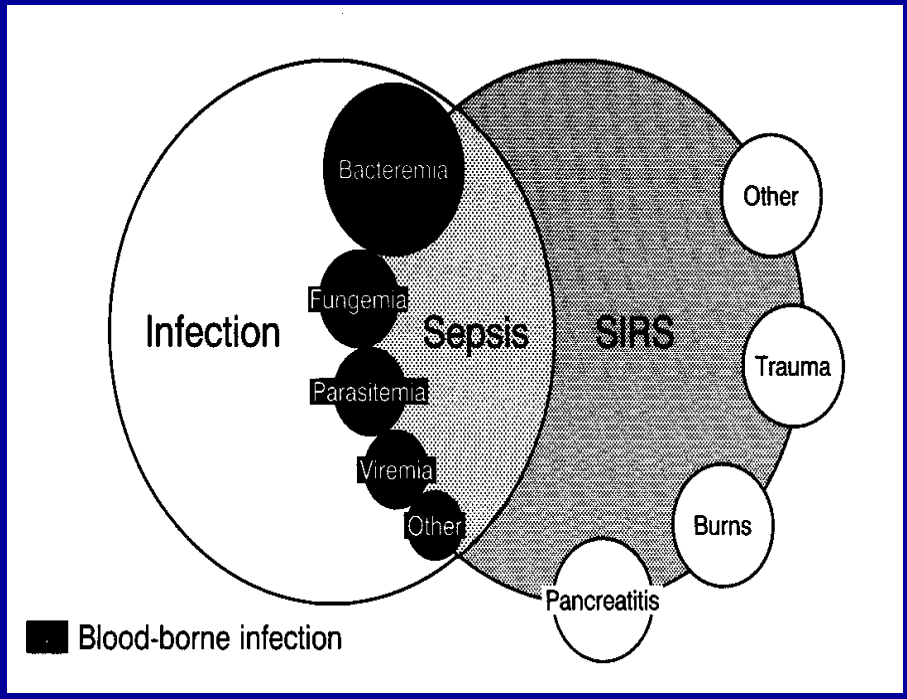
# Sepsis and Septic Shock: Current Management

Lawrence Lepler, MD

Pulmonary and Critical Care Medicine

# Sepsis: Definition

- SIRS - presence of 2 or more of the following:
  - Temp >38 or <36
  - HR >90
  - RR >20 or PaCO2 <32
  - WBC >12,000, <4,000, or >10% bands
- Sepsis - synonymous with SIRS when the process is due to an infection
- Severe sepsis - a/w hypoperfusion or hypotension
- Septic Shock - Hypotension despite fluid resuscitation with organ dysfunction
  - Hypotension -- SBP < 90 mm Hg or >or= 40 mm Hg decrease from baseline




Bone R, et al. C
rit Care Med 199

# Epidemiology of Sepsis

- 500,000 cases of sepsis per year
- 5-10 billion dollar cost
- Estimated mortality rate 35%
- 13th leading cause of death
- 6 month mortality is approximately equal to 30 day mortality

Rangel-Frausto, e
t al. Infect Dis

# Epidemiology of Sepsis

Table 2.—Frequency of Syndromes*

| Category | No. of Patients | Patients Surveyed, % | Patients With Sepsis, % |
|---|---|---|---|
| Total surveyed | 3708 | 100 | . . . |
| SIRS | 2527 | 68 | 100 |
| Sepsis | | | |
| Culture-positive | 649 | 17 | 26 |
| Culture-negative | 892 | 24 | 35 |
| Severe sepsis | | | |
| Culture-positive | 467 | 13 | 18 |
| Culture-negative | 527 | 14 | 21 |
| Septic shock | | | |
| Culture-positive | 110 | 3 | 4 |
| Culture-negative | 84 | 2 | 3 |

Rangel-Frausto, et al. JAMA 1995

# Epidemiology of Sepsis

| Syndrome | Prevalence Survey No. 1 | | Prevalence Survey No. 2 | |
|---|---|---|---|---|
| | Routinely Surveyed Wards (n=39†) | Routinely Nonsurveyed Wards (n=315†) | Routinely Surveyed Wards (n=41†) | Routinely Nonsurveyed Wards (n=334†) |
| SIRS | 64 (47-79) | 30 (25-35) | 61 (45-76) | 32 (27-37) |
| Sepsis | 8 (2-21) | 6 (4-10) | 20 (9-35) | 8 (5-11) |
| Severe sepsis | 3 (0.06-13) | 2 (0.5-4) | 0 | 3 (2-6) |
| Septic shock | 0 | 0 | 0 | 0 |

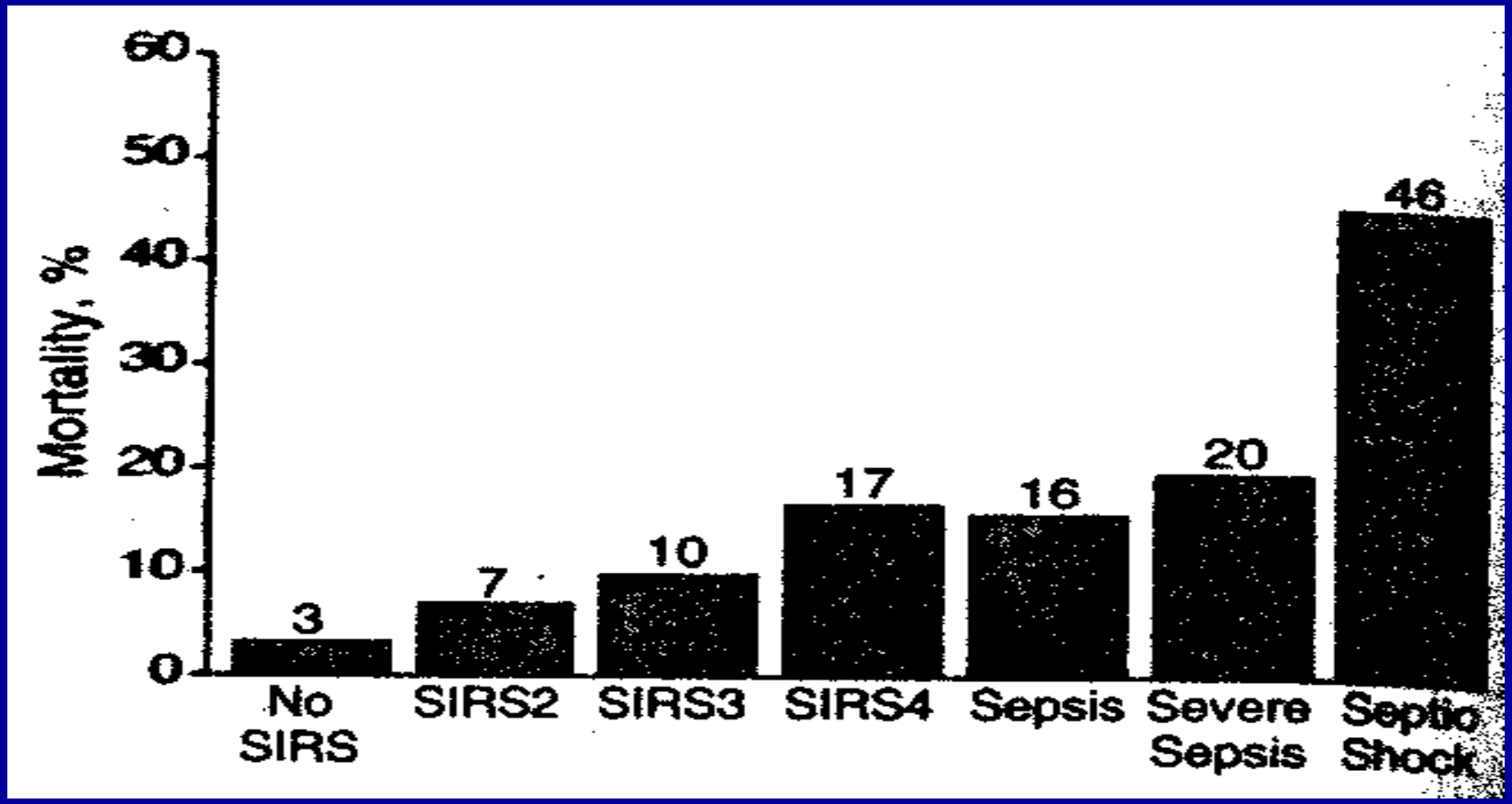
Rangel-Frausto, et al. JAMA 1995

# Incidence of End-Organ Dysfunction

| SYNDROME | ARDS, % | DIC, % | ACUTE RENAL FAILURE, % |
|---|---|---|---|
| SIRS – 2 Criteria | 2 | 8 | 9 |
| SIRS – 3 Criteria | 3 | 15 | 13 |
| SIRS – 4 Criteria | 6 | 19 | 19 |
| Severe Sepsis | 12 | 35 | 39 |
| Septic Shock | 36 | 38 | 89 |

Rangel-Frausto, et al. JAMA 1995

# Mortality




Rangel-Frausto, et al. JAMA 1995

# Cytokines & Anti-Cytokines

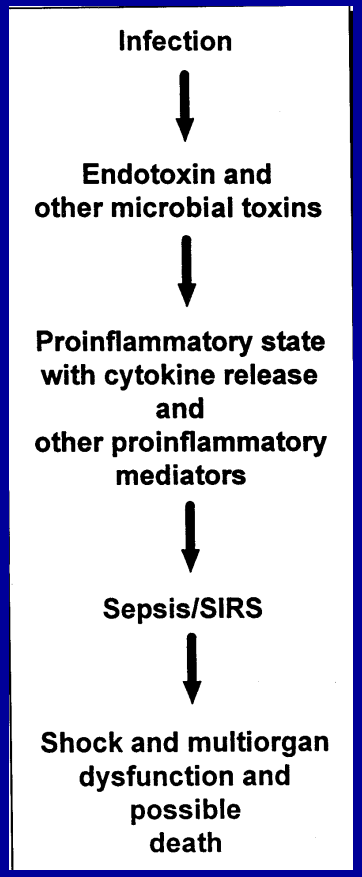
- 20 anti-inflammatory trials in sepsis
- All without success
- WHY?????

New Agents for Sepsis: A Summary of Prospective Randomized Trial Results*

| Agent | Source | Mortality | | |
|---|---|---|---|---|
| | | Treatment, % | Placebo, % | P |
| Methylprednisolone | Bone et al[1] | 34 | 25 | .06† |
| Glucocorticoid | Veterans Administration[2] | 21 | 22 | .97 |
| E5 monoclonal antibody to endotoxin | Bone et al[3] | 30 | 26 | .21 |
| E5 monoclonal antibody to endotoxin | Greenman et al[4] | 38 | 41 | .72 |
| Human monoclonal antibody HA-1A | McCloskey et al[5] | 33 | 32 | .86 |
| Human monoclonal antibody HA-1A | Ziegler et al[6] | 24 | 34 | .12 |
| Monoclonal antibody to human tumor necrosis factor-α | Abraham et al[7] | 30-31‡ | 33 | .33-.61 |
| Monoclonal antibody | Carlet et al[8] | 32-43‡ | 40 | .13-.45 |
| Monoclonal antibody | Reinhart et al[9] | 38-56‡ | 41 | . . .§ |
| Dimeric receptors | Sadoff et al[10] | 30-53‡ | 30 | .02† |
| Recombinant human interleukin-1 receptor antagonist | Fisher et al[11] | 29-31‡ | 34 | .22 |
| Platelet activating factor receptor antagonist BN 52021 | Dhainaut et al[12] | 42 | 51 | .17 |
| Platelet activating factor receptor antagonist BN 52021 | Dhainaut et al[13] | 44 | 50 | . . .§ |

Bone R. Why seps is trials fail?

# Cytokines & Anti-Cytokines


Infection
Endotoxin and other microbial toxins
Proinflammatory state with cytokine release and other proinflammatory mediators
Sepsis/SIRS
Shock and multiorgan dysfunction and possible death

# Cytokines & Anti-Cytokines

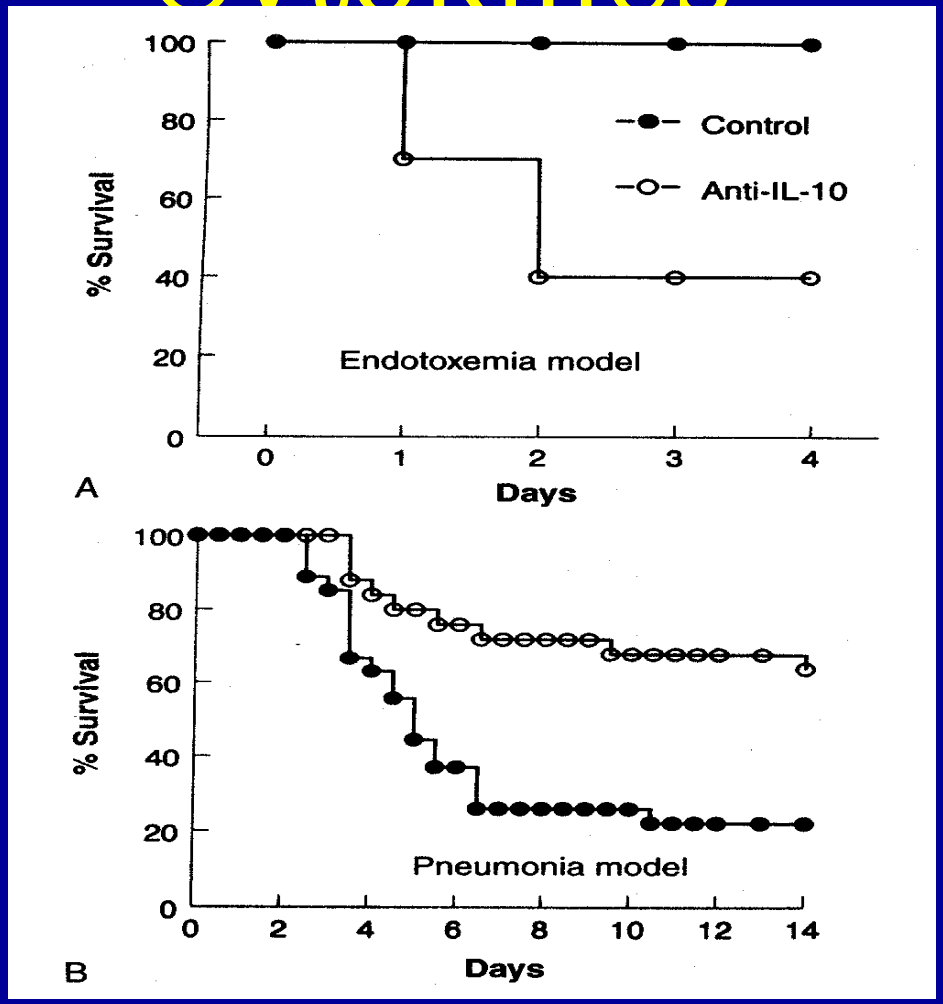
**Table 3—*Partial List of Proinflammatory and Anti-inflammatory Molecules***

| Proinflammatory Molecules | | Anti-inflammatory Molecules |
|---|---|---|
| TNF-α | Thromboxane | IL-1 ra |
| IL-1β | Platelet activating factor | IL-4 |
| IL-2 | Soluble adhesion molecules | IL-10 |
| IL-6 | Vasoactive neuropeptides | IL-13 |
| IL-8 | Phospholipase $A_2$ | Type II IL-1 receptor |
| IL-15 | Tyrosine kinase | Transforming growth factor-β |
| Neutrophil elastase | Plasminogen activator inhibitor-1 | Epinephrine |
| IFN-γ | Free radical generation | Soluble TNF-α receptors |
| Protein kinase | Neopterin | Leukotriene $B_4$-receptor antagonism |
| MCP-1* | CD14 | Soluble recombinant CD-14 |
| MCP-2 | Prostacyclin | LPS binding protein* |
| Leukemia inhibitory factor (D-factor) | Prostaglandins | |

*MCP=monocyte chemoattractant protein; LPS=lipopolysaccharide.

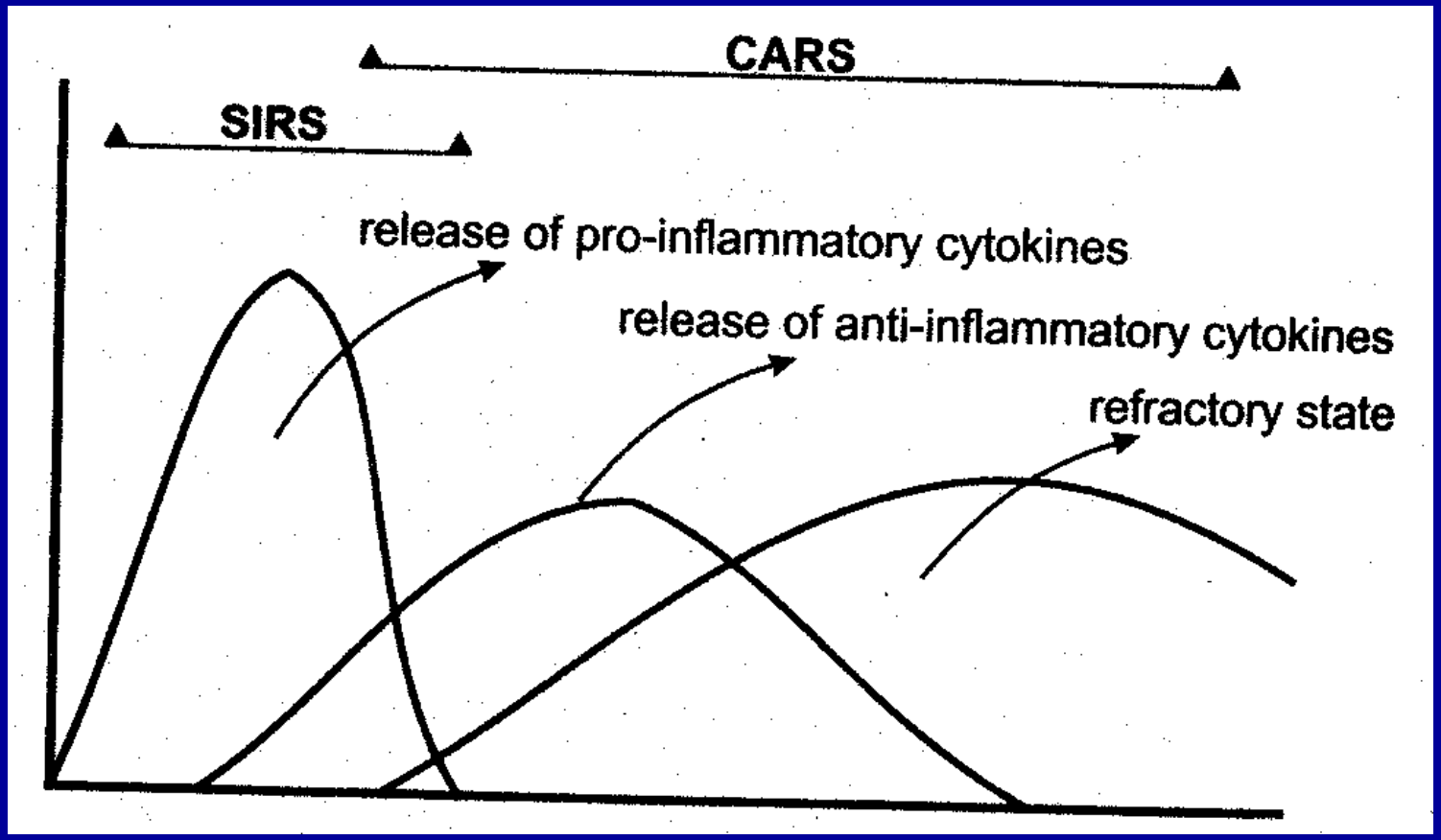
Bone R, et al. Se
psis: A new hypot

# Cytokines & Anti-Cytokines




van der Poll, et

# Cytokines & Anti-Cytokines



# Cytokines & Anti-Cytokines

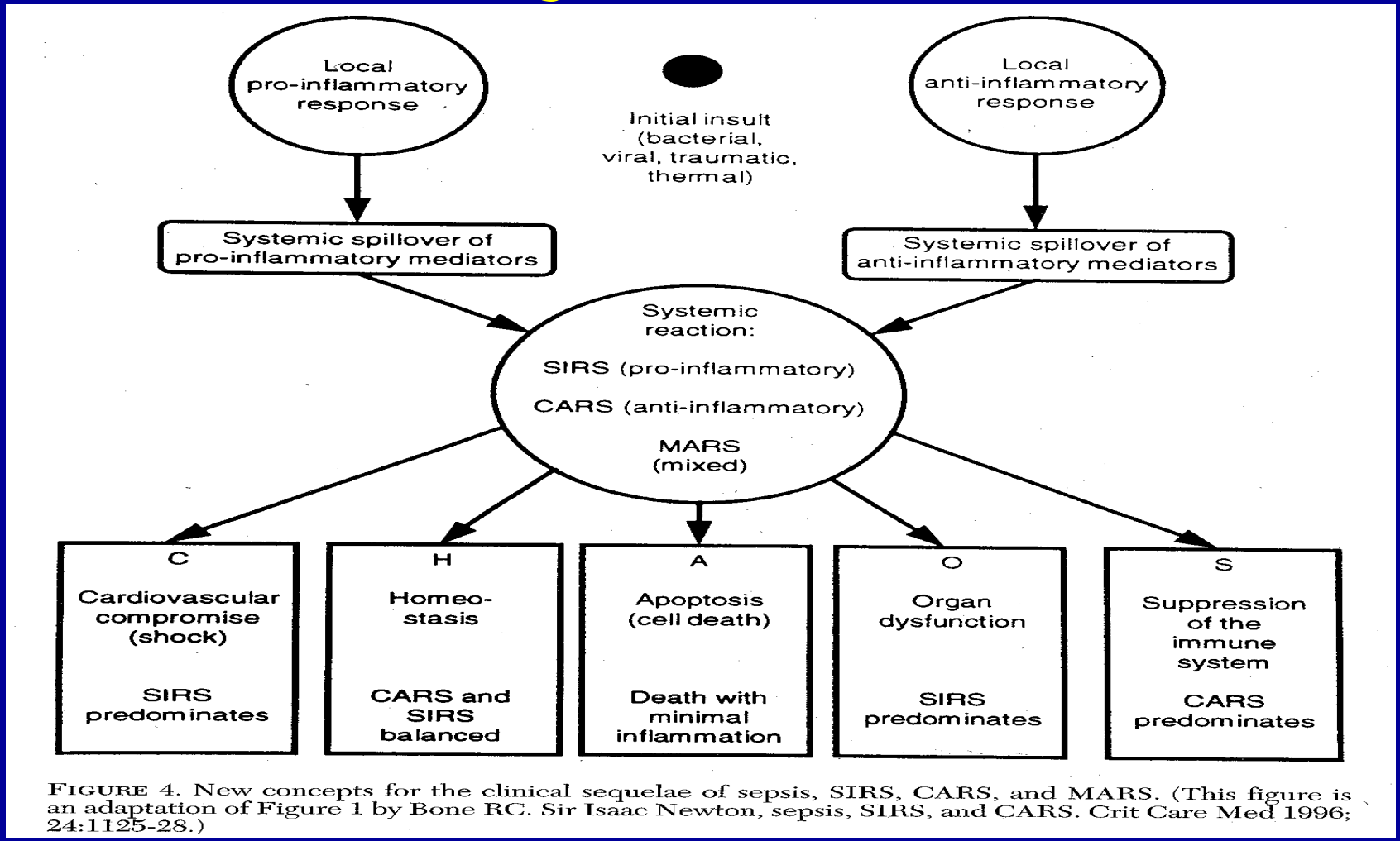
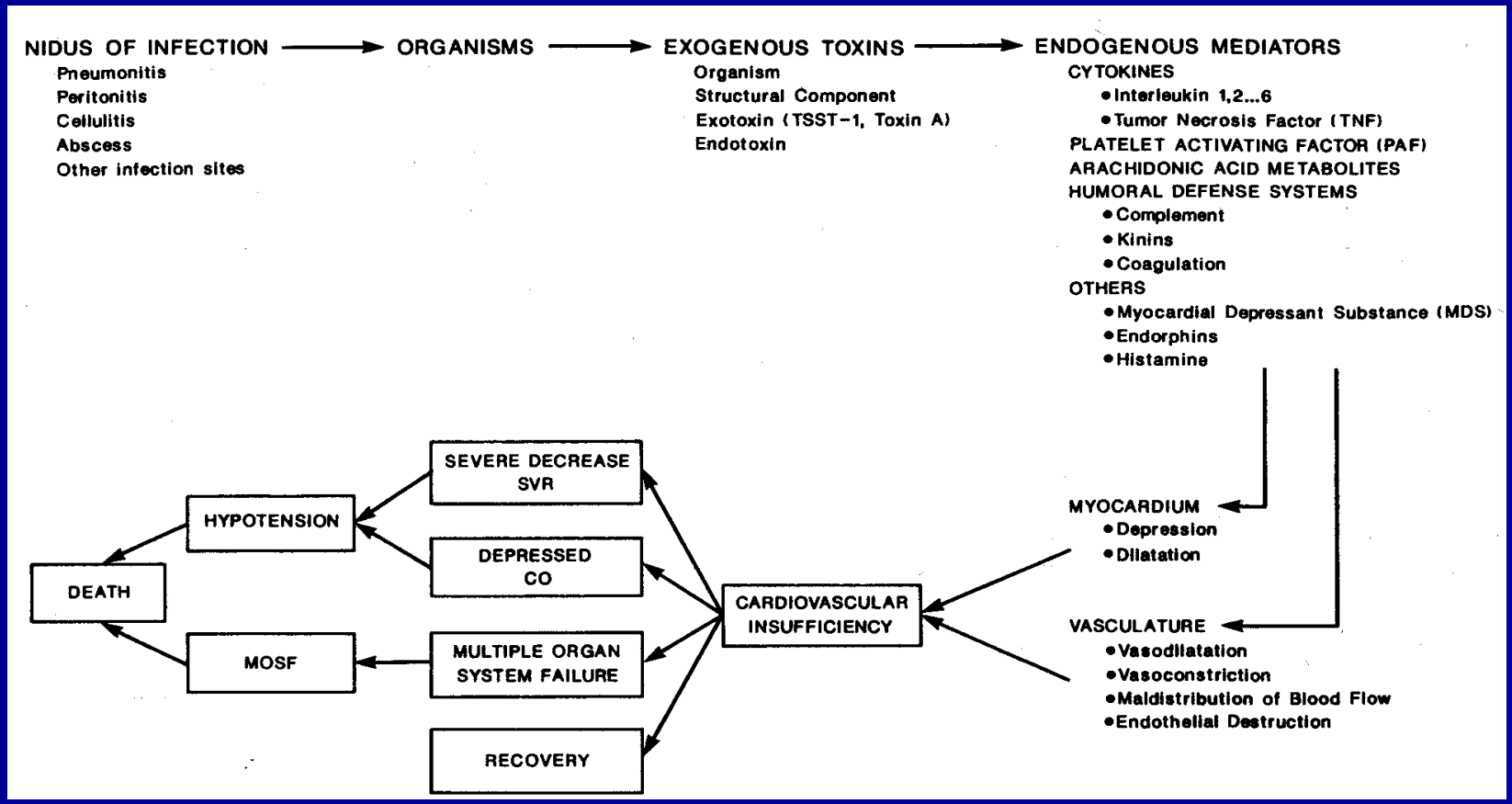


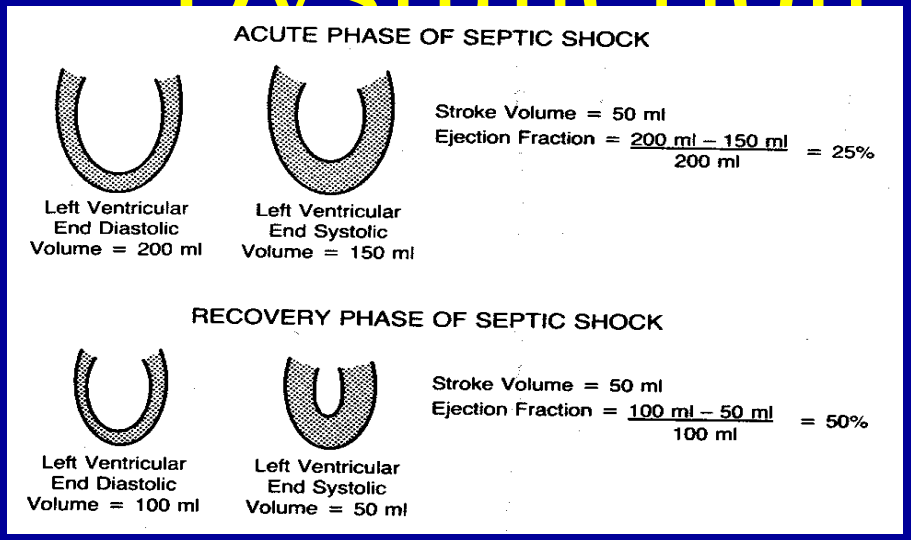

FIGURE 4. New concepts for the clinical sequelae of sepsis, SIRS, CARS, and MARS. (This figure is an adaptation of Figure 1 by Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med 1996; 24:1125-28.)

Bone R, et al. Se
psis: A new hypot

# Sepsis: Cardiovascular Dysfunction



# Cardiovascular Dysfunction


ACUTE PHASE OF SEPTIC SHOCK
Left Ventricular End Diastolic Volume = 200 ml
Left Ventricular End Systolic Volume = 150 ml
Stroke Volume = 50 ml
Ejection Fraction = 200 ml – 150 ml / 200 ml = 25%
RECOVERY PHASE OF SEPTIC SHOCK
Left Ventricular End Diastolic Volume = 100 ml
Left Ventricular End Systolic Volume = 50 ml
Stroke Volume = 50 ml
Ejection Fraction = 100 ml – 50 ml / 100 ml = 50%

- RIGHT SIDE
  - Pulmonary hypertension common
  - Contributes to right heart dysfunction
  - Myocardial depression
- LEFT SIDE
  - Low SVR; High CO
  - Maldistribution of blood flow
  - Compromised organ perfusion
  - Myocardial depression

Parrillo J, et al
Ann Intern Med

# Cardiovascular Dysfunction: Prognosis

- Hemodynamic profile associated with improved survival:
  - 1. Dilated LV with decreased EF
  - 2. Elevated CI that returns toward normal after 24 hours
  - 3. Return toward normal of mPAP and SVR.
  - 4. Low (< 5 mm Hg) PAD-PCWP gradient
- Cardiovascular abnormalities persist for 2-5 days and return toward normal over 1-2 weeks.

# Management

- Goals of Therapy
  - Restore tissue perfusion
    - MAP > or = 60 mm Hg
      - Consider premorbid blood pressure
    - Global and regional perfusion
      - Global
        - » MAP, Lactate, MVO2 saturation
      - Regional
        - » mental status, BUN/Cr, urine output, LFT's, pHi
  - Titrate to clinical endpoints not arbitrary values

# Management: Fluid Therapy

- Septic shock initially is hypovolemic with a low cardiac output.
- Volume resuscitation is associated with the development of a hyperdynamic state and improved survival.

# Management: Fluid Therapy

- Large fluid deficit - 6-10 liters
- 50% of hypotensive septic patients will respond to fluid alone.
- Optimal PCWP is typically 12-15 mm Hg
- Choice of fluid for resuscitation:
  - Crystalloid, 5% albumin, 6% hetastarch

# Management: Fluid Therapy

- Efficacy of fluid therapy
  - Crystalloids - 100-200 ml intravascular volume for each 1 liter
  - Colloids - 500-1000 ml intravascular volume for each 1 liter
- Therefore, 2-4 times more volume with cystalloids
- Colloids more expensive

# Management: Fluid Therapy

- Complications of fluid therapy
  - Increase interstitial edema
  - Increased hydrostatic pressure
  - Decreased colloid osmotic pressure
- Colloid infusion in sepsis does not increase pulmonary edema.
- When to use colloids?
  - Limited pulmonary reserve
  - PCWP > 15 mm Hg required

Fluid resuscitati
on in circulatory

# Management: Vasopressors

- Used when fluid therapy fails to restore adequate perfusion.
- Improve MAP without compromising stroke volume
- Attention to renal and splanchnic perfusion
- Dopamine, Norepinephrine, Epinephrine, Phenylephrine

# Management: Vasopressors

| | Norepinephrine | | | Dopamine | | | |
|---|---|---|---|---|---|---|---|
| | Baseline† | Nor‡ | Nor + 6 h‡ | Baseline§ | 25 μg‖ | Dop + Nor‖ | Dop + Nor + 6 h‖ |
| MBP, mm Hg | 54 ± 10 | 89 ± 13¶ | 91 ± 16¶ | 53 ± 8 | 59 ± 10 | 88 ± 8¶ | 89 ± 13¶ |
| HR, beat/min | 113 ± 21 | 112 ± 18 | 114 ± 21 | 110 ± 20 | 122 ± 21 | 128 ± 15 | 121 ± 14 |
| CI, L/min/m² | 5.3 ± 1.3 | 5.5 ± 1.2 | 5.4 ± 1.3 | 5.4 ± 1.1 | 5.5 ± 1.0 | 5.9 ± 1.6 | 5.3 ± 1.3 |
| PCWP, mm Hg | 12 ± 3 | 14 ± 4 | 15 ± 6 | 15 ± 6 | 16 ± 6 | 19 ± 12** | 17 ± 7 |
| SVRI, dyn.sec/cm⁵·m² | 659 ± 221 | 1,150 ± 350¶ | 1,278 ± 378¶ | 647 ± 197 | 659 ± 217 | 1,092 ± 337¶ | 1,235 ± 396¶ |
| MPAP, mm Hg | 24 ± 5 | 28 ± 5 | 29 ± 6 | 25 ± 5 | 27 ± 6 | 32 ± 9** | 32 ± 6** |
| $O_2$ ext | 0.26 ± 0.10 | 0.28 ± 0.10 | 0.29 ± 0.09†† | 0.23 ± 0.10 | 0.26 ± 0.09 | 0.25 ± 0.08 | 0.25 ± 0.06 |
| $IDO_2$, ml/min/m² | 801 ± 231 | 840 ± 225 | 836 ± 207 | 745 ± 206 | 697 ± 175 | 803 ± 227 | 743 ± 208 |
| $IVO_2$, ml/min/m² | 208 ± 70 | 232 ± 85†† | 235 ± 74†† | 178 ± 65 | 188 ± 65 | 197 ± 67 | 186 ± 51 |
| Urine output, ml/h | 22 ± 7 | 153 ± 51¶ | 189 ± 52¶ | 24 ± 6 | 8.2 ± 10 | 106 ± 100†† | 107 ± 125 |
| Lactate, mmol/L | 4.8 ± 1.6 | 4.4 ± 1.8 | 2.9 ± 0.8** | 4.8 ± 3.2 | 4.2 ± 2.0 | 3.8 ± 2.0 | 3.8 ± 3.0 |

- Norepinephrine more potent and more predictable at restoring MAP
- No compromise in cardiac performance or oxygen delivery.

Norepinephrine o
r dopamine for t

# Management: Vasopressors

Table 3.—Hemodynamic and Oxgenation Data of Patients Treated With Norepinephrine or Dopamine (Mean±SEM)

| | Norepinephrine (n=10) | | | Dopamine (n=10) | | | Changes at 3 Hours, P* |
|---|---|---|---|---|---|---|---|
| | Baseline | 3 Hours | P | Baseline | 3 Hours | P | |
| Heart rate, beats/min | 105±5 | 102±3 | .20 | 121±4 | 139±3 | .001 | .002 |
| Mean arterial pressure, mm Hg | 65±4 | 87±4 | <.001 | 63±2 | 87±3 | <.001 | .60 |
| Mean pulmonary arterial pressure, mm Hg | 27±3 | 31±2 | .03 | 29±2 | 34±3 | .005 | .70 |
| Pulmonary capillary wedge pressure, mm Hg | 15±1 | 16±1 | .20 | 15±1 | 16±1 | .10 | .70 |
| Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$ | 4.2±0.5 | 4.7±0.4 | .01 | 4.2±0.4 | 5.3±0.7 | .008 | .05 |
| Right ventricular ejection fraction | 28.6±3.2 | 31.1±3.0 | .008 | 28.4±3.4 | 33.3±3.71 | .02 | .50 |
| Left ventricular stroke work index | 29±4 | 44±7 | .007 | 25±4 | 37±5 | <.001 | .50 |
| Systemic vascular resistance index, $dyne \cdot s \cdot cm^{-5} \cdot m^{-2}$ | 1110±109 | 1405±107 | .005 | 1035±77 | 1221±130 | .10 | .60 |
| Oxygen delivery index, $mL \cdot min^{-1} \cdot m^{-2}$ | 498±77 | 569±68 | .02 | 573±54 | 703±89 | .02 | .20 |
| Oxygen consumption index, $mL \cdot min^{-1} \cdot m^{-2}$ | 145±21 | 162±22 | .05 | 183±29 | 221±38 | .001 | .20 |
| Intramucosal pH | 7.16±0.07 | 7.23±0.07 | .008 | 7.24±0.04 | 7.18±0.05 | .02 | <.001 |
| Lactate, mmol/L | 1.8±0.5 | 1.9±0.43 | .60 | 2.2±0.4 | 2.1±0.4 | .60 | .60 |

*Difference between the 3-hour values of dopamine and norepinephrine correcting for baseline values.

- No significant difference in most hemodynamic variables and oxygen delivery
- Improved pHi with norepinephrine; worsened pHi with dopamine

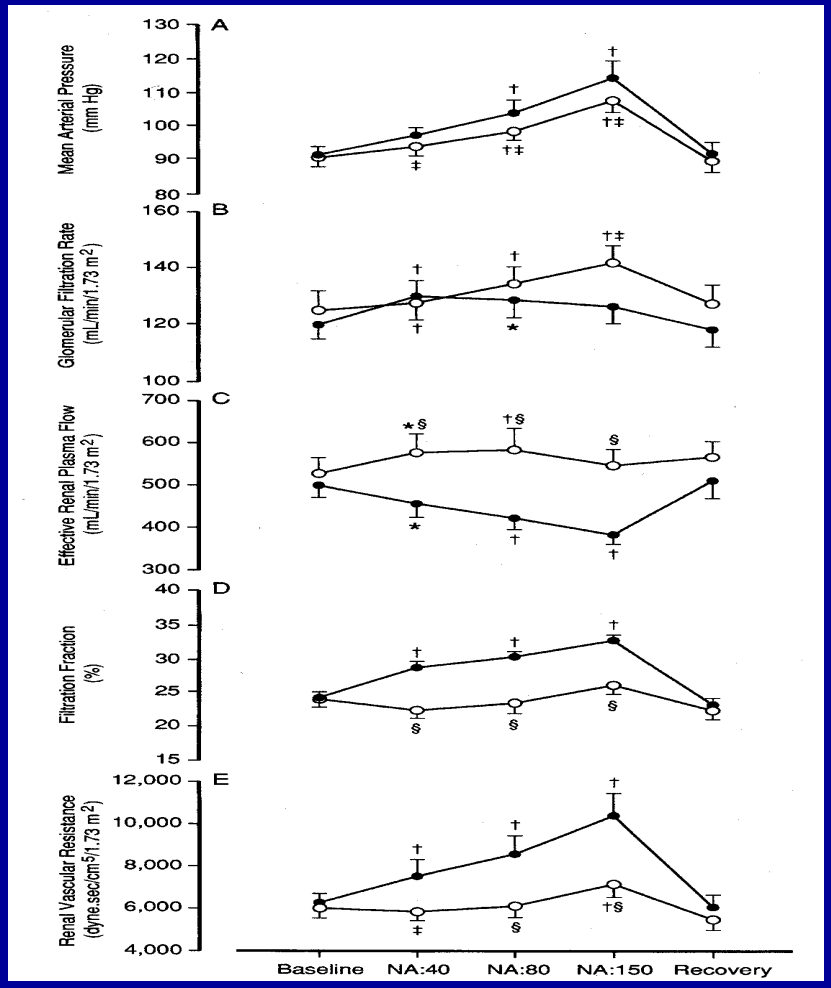
Marik PE, et al.
JAMA 1994; 272:

# Management: Vasopressors

- Dopamine
  - Systemic hemodynamics
    - Improved
  - Urine Output
    - Improved
  - pHi / gastric mucosal blood flow
    - Worsened???
- Norepinephrine
  - Systemic hemodynamics
    - Improved
  - Urine Output
    - Improved
  - pHi / gastric mucosal blood flow
    - Improved???
- Patient must be volume resuscitated

# Management: Renal Dose Dopamine

- Safety of norepinephrine shown while on low dose dopamine
- Studies show preservation of renal perfusion with low dose dopamine




Hoogenberg K, et al. Crit Care M

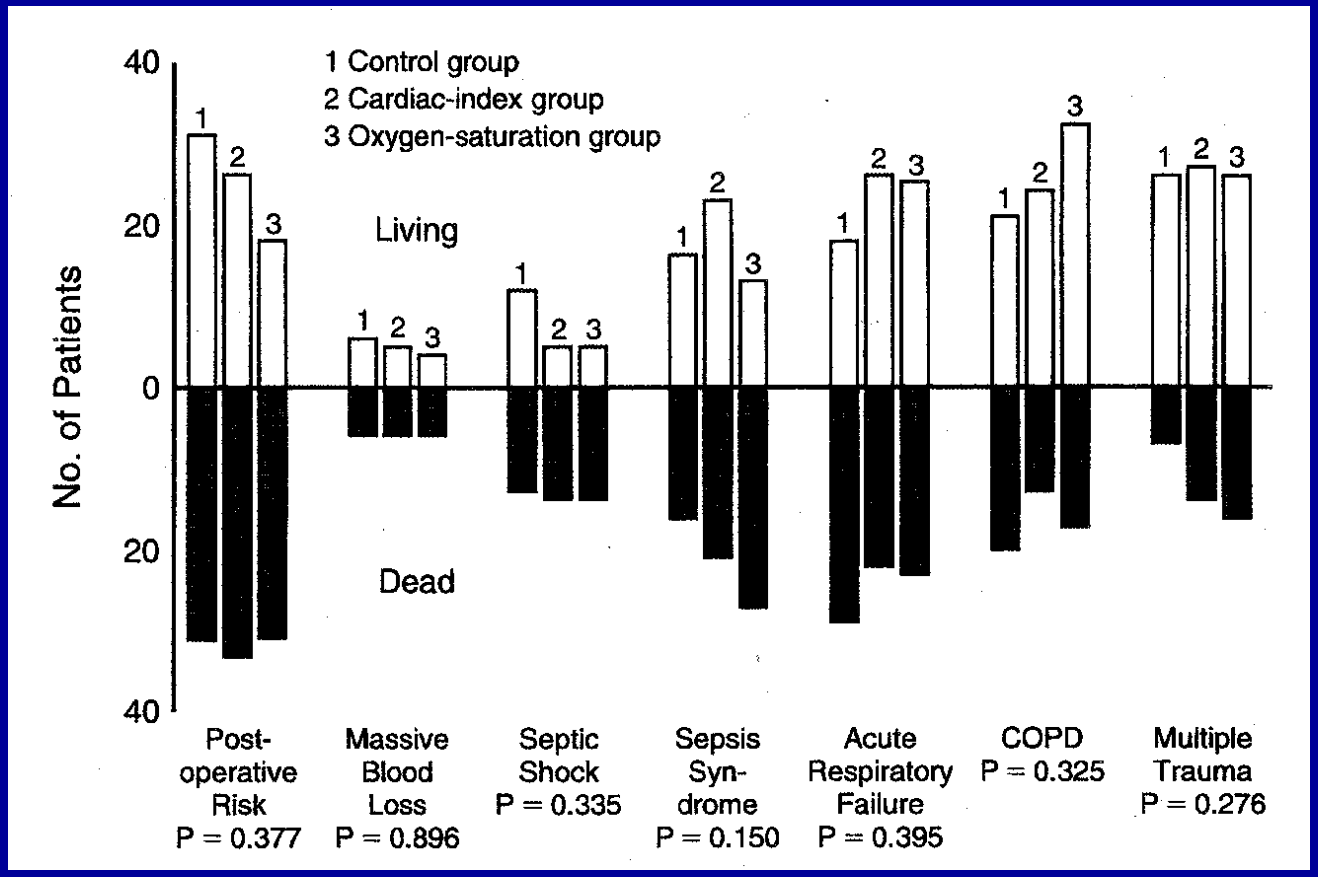
# Management: Vasopressors

- Epinephrine
  - Can increase MAP in patient unresponsive to dopamine and norepinephrine
  - Associated with decreased gastric mucosal blood flow and increased serum lactate
    - Addition of dobutamine ???
- Phenylephrine
  - Useful in  cases of excessive tachyarrhythmias

# Management: Inotropes

- Myocardial dysfunction with sepsis
- Survivors of critical illness had inherently higher CI and DO2
- Led to several trials of increasing CI and DO2 in an effort to improve survival
- These several trials had two major findings:
  - It can be difficult to achieve hemodynamic objectives
  - Increasing CI and DO2 does not improve survival

# Management: Inotropes

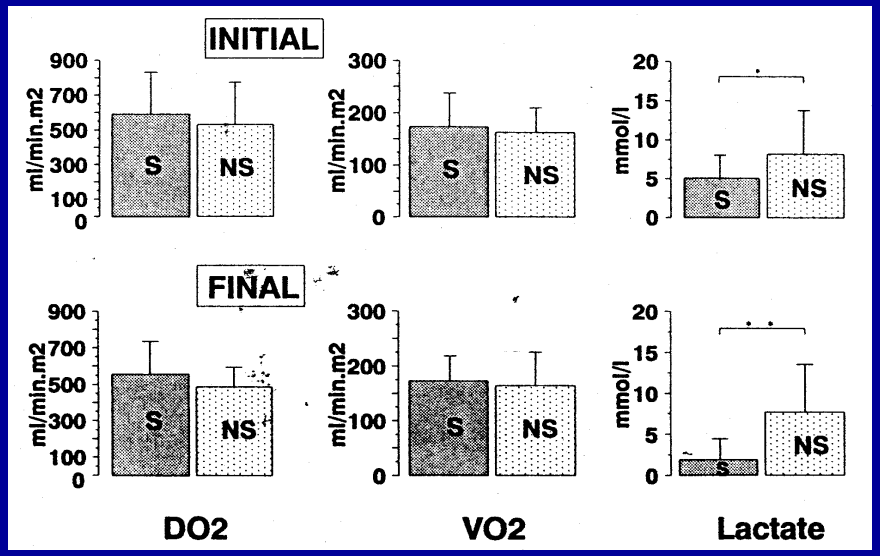



Gattinoni L, et a
l. N Engl J Med 1

# Management: Inotropes

- Inotropic agents should be titrated to:
  - SVO2 < 65%
  - Lactate
  - Urine output
  - Cardiac Index < 2.5 L/min/$m^2$

# Management: Inotropes




- Serum lactate has prognostic significance
- The trend is a better predictor than a single value
- Lactate is a better prognostic indicator than oxygen derived variables septic shock

Bakker J, et al.
Chest 1991; 99:95

# Corticosteroids and Sepsis

- High dose steroid in sepsis and septic shock failed to show survival advantage.
- Increased mortality in patients with renal failure.
- Evidence of relative adrenocortical insufficiency in patients with septic shock.

# Corticosteroids and Sepsis

- Two studies
  - Cortisol dose roughly 300 mg/day
  - Decreased time to shock reversal
  - Trend toward improved survival vs. no change in survival

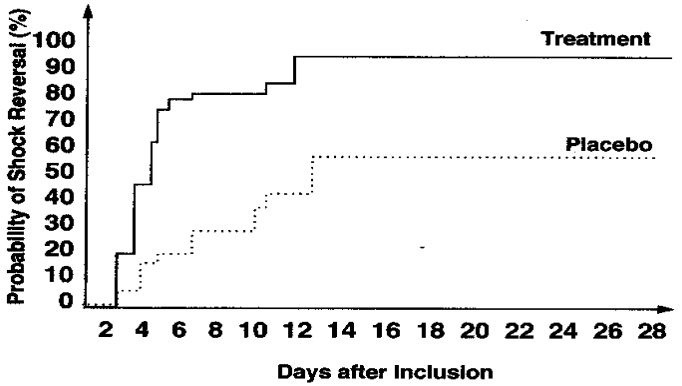



**Figure 2.** Kaplan-Meier estimates of 28-day reversal of shock.

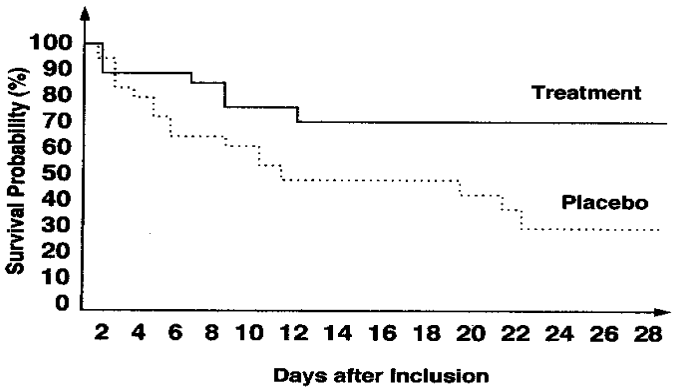



**Figure 3.** Kaplan-Meier estimates of 28-day all-cause mortality.

Bollaert PE, et a
l Crit Care Med

# Summary

- 1. **Epidemiology** - Common problem with high mortality
- 2. **Cytokines And Anticytokine Therapy** - No magic bullet but a new paradigm for understanding the pathogenesis
- 3. **Cardiovascular Response to Sepsis -** Impaired cardiac function with some prognostic features
- 4. **Therapeutics**
  - **Fluids -** Crystalloid first. There is a role for colloid
  - **Vasopressors and Inotropes** - There not all created equal. Norepinephrine may have an advantage in volume replete patient No role for driving DO2. Lactate is a useful prognosticator.
  - **Steroids -** More to come. May have a role in persistent shock state.

Practice paramet
ers for hemodyna